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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/187,385	11/06/98	MARKOVIC S	07039/119001

HM12/0828

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EXAMINER	
HOLLERAN, A	
ART UNIT	**PAPER NUMBER**
1642	8

DATE MAILED: 08/28/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/187,385	Markovic, S.N.
Examiner	**Group Art Unit**
Anne Holleran	1642

☒ Responsive to communication(s) filed on *Jun 5, 2000*

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-12, 15, 16, and 18-26* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12, 15, 16, and 18-26* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

1. This communication is responsive to the Amendment filed June 5, 2000.

Claims 13, 14 and 17 were canceled.

Claims 1-12, 15, 16, and 18-26 are pending and examined on the merits.

Priority

2. Upon further consideration, priority under 35 U.S.C. 119(e) for claims 10-12 is granted.

Drawings

3. The objection to the drawings is held in abeyance.

Claim Rejections - 35 USC § 112, second paragraph

4. The rejection of Claims 17-20 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of the amendment canceling claim 17. The rejection of claims 24 and 25 under 35 U.S.C. 112, second paragraph is made and maintained. New grounds for making the rejection are presented:

Claims 24 and 25 are vague and indefinite because it is not clear how the immunostimulatory dosage of the alpha-interferon results in treatment of a patient having a malignant tumor. Thus, it is not clear what information is included in the label or package insert.

5. The rejection of Claims 13 and 14 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in view of the Amendment canceling claims 13 and 14.

6. The rejection of Claims 24 and 25 under 35 U.S.C. 102(b) as being anticipated by Ucar et al. (Ucar, R. et al., Annals of Allergy, Asthma, and Immunology, 75: 377-386, 1995; IDS Ref. "DI") is maintained. Upon reconsideration, the new grounds for the rejection of claims 24 and 25 under 35 U.S.C. 102(b) are presented.

Claims 24 and 25 are drawn to articles of manufacture comprising α-interferon compositions and labels or package inserts which indicates that administration of an immunostimulatory dosage of a-interferon can be effective in treating a human patient having a resectable or non-resectable malignant tumor. For examination purposes, the label or package insert elements of the claimed articles of manufacture are considered to be intended use limitations. An intended use limitation is given patentable weight to a claim for a product if it results in a structural difference in the claimed product (MPEP 2111.02). Furthermore, the recitations describing the information contained in the label or package insert does not clearly state that a specific dose is to be used and only states that administration of a-interferon "can be" effective for treatment of a malignant tumor.

As Ucar et al disclose three commercial preparations of α-interferon (page 380, 3rd column and Table 4) and that these preparations are useful clinically, Ucar et al disclose articles of manufacture which are the same as that claimed.

7. The rejection of Claim 26 rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent 4,846,782 (published Jul. 11, 1989 to Bonnem; IDS Ref. "AA") is maintained.

Applicant's arguments have been considered but not found persuasive. Claim 26, now amended to recite a dose range of "about 1,000,000 U/m^2" does not free the claimed method from the prior art of record because it is not clear what range is encompassed by "about 1,000,000 U/m^2". Bonnem discloses administering a minimum dose of 2,000,000 U/m^2. It is not clear from the specification that about 1,000,000 U/m^2 is different from 2,000,000 U/m^2.

8. The rejection of Claims 1, 7, 8 and 15-22 under 35 U.S.C. 103(a) as being unpatentable over Markovic et al[a] (Markovic, S.N. et al., Int. J. Cancer, 45: 788-794, 1990; IDS Ref. "CH") in view of either Golub et al (Golub, S.H. et al., J. Nat. Cancer Inst., 68: 703-710, 1982; IDS Ref. "AO"), Toliou et al. (Toliou, Th. et al, Eur. Urol, 29: 252-256, 1996; IDS Ref. "DH") or Neefe et al. (Neefe, J.R. et al., Cancer Res., 45: 874-878, 1985) is made again and maintained. In addition, upon further consideration, claims 2-6 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Markovic et al[a] (Markovic, S.N. et al., Int. J. Cancer, 45: 788-794, 1990; IDS Ref. "CH") in view of either Golub et al (Golub, S.H. et al., J. Nat. Cancer Inst., 68: 703-

710, 1982; IDS Ref. "AO"), Toliou et al. (Toliou, Th. et al, Eur. Urol, 29: 252-256, 1996; IDS Ref. "DH") or Neefe et al. (Neefe, J.R. et al., Cancer Res., 45: 874-878, 1985).

Applicant's arguments have been considered but not found persuasive. Applicant states that Markovic et al [a] does not provide the legally required reasonable expectation of success in treating human patients by administering 4,000,000U/m^2 of α-interferon before surgery to remove a resectable tumor and states that the trend in Markovic et al [a] is to escalate the dose of α-interferon. However, this argument is not found persuasive because there are no teachings in Markovic et al that would suggest that a maximum effective dose for mice had been found. Thus, the observation that the higher of two doses used in mice was more effective than the lower dose cannot be extrapolated to a conclusion that a reference teaches that ever increasing doses of an agent will always have a beneficial effect.

The most important teaching of Markovic et al is that α-interferon acts to increase NK cell activity and cytolytic T-cell responses and that the increased NK cell activity and cytolytic T-cell responses are associated with the superior therapeutic efficacy of neo-adjuvant α-interferon treatment.

The teachings of Golub et al, Toliou et al and Neefe et al all support a conclusion that one of ordinary skill in the art would have had a reasonable expectation of success in making the claimed methods as it applies to human patients because each of the references teaches an increased immune function in humans due to treatment with α-interferon. Thus, the prior art as a whole suggests the claimed invention because Markovic et al teaches the claimed methods in mice and any of Golub et al, Toliou et al or Neefe et al demonstrate that human immune function is

stimulated by α-interferon. As to the limitation that the immunostimulatory dosage be about 4,000,000 U/m^2 or less, 1,000,000 U/m^2 , 500,000 U/m^2, 250,000 U/m^2, 100,000 U/m^2, it would have been within the skill of the ordinary artisan at the time the invention was made to have determined effective doses that provided immunostimulatory activity with the least amount of side effects.

9. The rejection of Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Markovic et al [b] (Markovic, S.N. et al., Clinical Immunology and Immunopathology, 60: 181-189, 1991; IDS Ref. "CF") in view of either Golub et al (supra), Toliou et al. (supra") or Neefe et al. (supra) is maintained.

Applicant's arguments have been considered but not found persuasive. Applicant states that the teachings of Markovic et al[b] do not suggest the claimed invention. However, Markovic et al [b] clearly suggests that exposure to anesthesia may predisposes one to post-operative infections (page 187) and supports this theory by demonstrating that anesthesia reduces natural killer cell activity in mice. Furthermore Markovic et al [b] demonstrates that α-interferon administration before surgery prevents the reduction in natural killer cell activity. That there is a reasonable expectation that these results can be extrapolated to cancer patients is shown by any of the teachings of any of Golub et al, Toliou et al or Neefe et al, demonstrating that in human cancer patients α-interferon induces increases immune function, specifically, that it increases natural killer cell activity. As to the argument that the prior art does not teach the specific dose range of 4,000,000 U/m^2 per day or less, it would have been within the skill of the ordinary artisan

at the time the invention was made to have determined effective doses that provided maximal immunostimulatory activity with the least amount of side effects.

New Grounds of Rejection:

10. Claims 1-12, 15, 16 and 18-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it is not clear how the recited method steps result in a treatment of a human patient. Although it is obvious that resection of a tumor is a treatment for a cancer patient, it is not clear how the administration of an immunostimulatory dosage is a treatment for a patient having a resectable malignant tumor. It is not clear what is being treated as the resection of the resectable tumor is already a treatment for a patient having a resectable tumor.

Claims 1 and 23-26 are vague and indefinite because they refer to open ended dose ranges by the use of "or less". It is not clear how much less and as currently recited the claims could be drawn to methods were a dose of 0 U/m^2 is used.

Claims 1-7, 9-12, 23-26 are vague and indefinite because of the use of "about". It is not clear from the claim or from the teachings in the specification how much variation is meant by the term "about".

Claims 15 and 16 are vague and indefinite because they are drawn to methods wherein the immunostimulatory dosage increases T-lymphocyte activation or function. It is not clear if the

increase in T-lymphocyte activation or function is in addition to increasing the NK lymphocyte activity or instead of increasing NK lymphocyte activity. It is noted that the disclosure of the specification defines "immunostimulatory dosage" as an interferon dosage that increases NK lymphocyte cytotoxicity in a human (page 8, lines 25-27).

Claim 15 is vague and indefinite because it is not clear how merely activating T-lymphocytes results in treatment of a patient as "T-lymphocyte activation" appears to be functionally different from "T-lymphocyte function" (of claim 16).

Claims 23 is vague and indefinite because it is not clear how the recited method steps result in preventing post-operative infection. Claim 23 appears to be lacking a correlative step that associates the preamble of the claim with the recited method steps.

Claim 26 is vague and indefinite because it is not clear how the recited steps result in a treatment of a human patient having a non-resectable malignant tumor. Furthermore, it is not clear what is encompassed by "effective non-surgical medical methodologies".

11. Claims 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification;

3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

Claims 15 and 16 are drawn to methods of treating a patient having a resectable malignant tumor comprising administering an immunostimulatory dosage of α-interferon which results in either the activation or increased function of T-lymphocytes and then surgically resecting the malignant tumor. The immunostimulatory dosage is about 4,000,000 U/m2 or less.

The disclosure of the specification does not support the claimed invention as broadly drawn to methods of treating a human with a resectable malignant tumor by administering an immunostimulatory dosage of α-interferon which increases the activation or function of any type of T-lymphocytes. While the art teaches that increasing the activity of cytotoxic T-lymphocytes would be helpful in an antitumor response, it is not clear how activation of the many other types of T-lymphocytes would be useful in treating a patient having a resectable tumor. The specification does not provide teachings or data indicating which types or if all types of T-lymphocytes are activated and exhibit increased functioning with the administration of α-interferon. Nor does the specification teach or disclose how increase functioning of specific T-cell types may be used in the claimed invention. In view of the fact the T-lymphocytes encompasses a variety of functionally diverse cell types (Roitt et al., Immunology, 3rd edition, Mosby, St. Louis, 1993; pages 2.5 - 2.7) and that cytotoxic lymphocytes are not representative of all of the different types of T-lymphocytes, one of skill in the art would not be able to practice the claimed invention commensurate in scope with that of claims 15 and 16.

12. Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 23 is drawn to a method of preventing a post-operative infection comprising administering an immunostimulatory dosage of α-interferon before surgery. The art defines infection as "multiplication of parasitic organisms within the body (see Stedman's Medical Dictionary, 24th edition, Williams and Wilkins, Baltimore, 1982, page 707). Thus, as little as a single round of multiplication of a single organisms would constitute an "infection".

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

The claimed method reads on methods to prevent any degree of infection. While the specification teaches that α-interferon stimulates the immune system and the prior art teach that a-interferon is useful for reducing the spread of viral infection (Roitt et al., Immunology, 3rd edition, Mosby, St. Louis, 1993; page 1.6), it is not clear from the specification how interferon may be used in a method for absolute prevention of an infection, given the broad definition of infection. In view of the breadth of the claimed method and in view of the variability in the what is meant by preventing an infection, one of skill in the art would not have a reasonable expectation

of success without undue experimentation in practicing the claimed method of "preventing" a post-operative infection.

13. Claims 1-6, 18-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lennard et al (Lennard, T.W. et al., Br. J. Surgery, 72(10): 771-776, 1985).

Claims 1-6, 18-22 are drawn to methods of treating a patient having a resectable malignant tumor comprising administering α-interferon before surgery. Claim 23 is drawn to a method of preventing a post-operative infection comprising administering α-interferon before surgery. For purposes of examination, claim 23 is interpreted to read on methods of reducing post-operative infection.

Lennard et al teaches that surgical trauma has immunosuppressive effects on surgical patients and that this may decrease defenses against tumor cells (see page 771-772, bridging paragraph and page 774, 2nd column, 1st paragraph). Lennard et al suggest pre-operative administration of interferon. Thus, it would have been obvious to one of ordinary skill in the art to have made the claimed methods of treating patients or of reducing post-operative infection, comprising administering α-interferon and then surgically removing a resectable malignant tumor, and the claimed articles of manufacture, at the time the invention was filed. As to the specific dose range of 4,000,000 U/m^2 per day or less, it would have been within the skill of the ordinary artisan at the time the invention was made to have determined effective doses that provided maximal immunostimulatory activity with the least amount of side effects.

Conclusion

No claim is allowed. As new grounds of rejection are presented, this rejection is not made final.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

ALH

Anne L. Holleran
Patent Examiner
August 25, 2000

Brenda Brumback
BRENDA BRUMBACK
PATENT EXAMINER